Journal of Renal and Hepatic Disorders

REVIEW ARTICLE

Wasting Away with Cirrhosis: A Review of Hepatic Sarcopenia

Ernesto Robalino Gonzaga[1], Austin Andrew[2], Freeman Jan George[2]

[1]Department of Internal Medicine, University of Central Florida College of Medicine, Orlando, FL, USA
[2]Hepatology Unit, University Hospitals of Derby and Burton on Trent, Derby, United Kingdom

Abstract

The complications of decompensated cirrhosis are well documented and include variceal bleeding, fluid retention, and hepatic encephalopathy. A less well recognized complication of cirrhosis is muscle wasting or sarcopenia. It is now recognized to have a significant impact on patient survival, especially in patients who are awaiting liver transplantation. An understanding of the pathophysiology of muscle protein homeostasis has led to several proposed mechanisms of sarcopenia and the potential to reverse muscle loss. This review discusses the potential mechanisms of sarcopenia and highlights the possible future means of reversing sarcopenia.

Keywords: sarcopenia; cirrhosis; wasting; end-stage liver disease; muscle

Received: 14 June 2019; *Accepted after revision*: 30 July 2019; *Published*: 09 September 2019

Author for correspondence: Freeman Jan George, Hepatology Unit, University Hospitals of Derby and Burton on Trent, Derby, DE22 3NE, United Kingdom. Email: j.freeman115@btinternet.com

How to cite: Gonzaga ER et al. Wasting away with cirrhosis: a review of Hepatic Sarcopenia. J Ren Hepat Disord. 2019;3(1):40–46.

Doi: http://dx.doi.org/10.15586/jrenhep.2019.56

Introduction

Malnutrition is a common finding in end-stage liver disease (ESLD) (1), leading to a loss of muscle mass and an increase in frailty. The causes of malnutrition include inadequate dietary intake, anorexia, malabsorption, low salt and protein diets offered, and the complications of ESLD such as encephalopathy and ascites. ESLD patients with malnutrition have longer hospital stays, increased hepatic complications, and in-hospital mortality (2). Loss of muscle mass, sarcopenia, is not synonymous with malnutrition although they often overlap. Sarcopenia is a common complication of cirrhosis and is frequently overlooked. It is defined as a reduction in the skeletal muscle mass and strength. It is often not addressed as a prognostic factor in ESLD or in patients assessed for liver transplantation. The mechanisms behind the cause of sarcopenia are not fully understood, but it is a complication that adversely affects ESLD patient's survival and quality of life. The prevalence of sarcopenia is higher than any other complications of ESLD. The mean prevalence is 48% compared to esophageal varices (10–15%), refractory ascites (−10%), or hepatocellular cancer (3, 4). There appears to be some gender and ethnicity factors in the development of sarcopenia, with it being more prevalent in Western societies (5). The prevalence of sarcopenia in cirrhosis is higher than any other gastrointestinal disorder, being only 21% in patients with inflammatory bowel disease (4). The aim of this review is to assess the current state of knowledge of the mechanisms of muscle wasting in liver disease, diagnostic issues, and potential therapies.

Body Composition and Muscle Physiology

In order to assess the loss of muscle mass, it is important to have an understanding of relative body composition and muscle physiology in a healthy individual. The assessment of body composition and of somatic protein stores relies on measuring the different body compartments, that is, water, fat, bone, muscle, and visceral organs. Body composition techniques aid in the diagnosis of protein depletion. Protein levels are usually preserved at the expense of fat utilization as an energy source. The amount of body fat compared to muscle volume varies according to the cirrhotic stage. In compensated cirrhotics, there is a high amount of body fat. While in decompensated cirrhotics there is a much lower amount of body fat, implying lipolysis occurring in the latter stages of cirrhosis is an alternative energy source (6). The utilization of fat thus spares muscle in the early stages of cirrhosis but as it becomes depleted glycogenesis in the muscle leads to a rapid muscle breakdown leading to sarcopenia. The assessment of body composition ranges from simple anthropometric tests such as skin thickness to more complex measures such as bioelectrical impedance. Measuring such composition is essential when evaluating malnutrition and sarcopenia in liver patients.

The homeostasis of muscle bulk is tightly regulated requiring a balance between muscle protein synthesis and muscle proteolysis. Muscle protein synthesis and muscle satellite cell recruitment are important factors in maintaining muscle bulk. The major pathway regulating protein synthesis is the exercise activation of mammalian target of rapamycin (mTOR). Recent evidence suggests that exercise increases intracellular calcium levels triggering both mTOR and mitogen-activated protein kinase (MAPK) to stimulate muscle protein formation (7). Other suggested stimuli of muscle protein production include insulin-like growth factor (IGF-1), insulin, leucine, testosterone (8), and interleukin (1).

Muscle replacement requires the activation and recruitment of muscle satellite cells, the adult stem cell of skeletal muscle located between the sarcolemma and basal lamina within the muscle tissue. When activated they proliferate to expand the population of myoblasts and differentiate into myotubes capable of fusing together to form new myofibers.

Muscle protein synthesis and satellite cell recruitment are negatively controlled by the cytokine myostatin. Myostatin belongs to the transforming growth factor beta family. Acting in a paracrine fashion, its action is via a linkage with activin(s), which is a type 2 transmembrane receptor leading to a serine threonine kinase phosphorylation of Smad2/3 that in turn transcriptionally regulates target genes responsible for muscle protein synthesis. To maintain muscle homeostasis, myostatin levels are regulated by follistatin, a widely expressed glycoprotein acting as an extracellular ligand trap to regulate the availability of myostatin and activins. Its actions are to increase/activate satellite cell recruitment and inhibit Smad2/3, thereby negating the action of myostatin. In experimental models, follistatin infusions increase muscle protein synthesis leading to muscle hypertrophy (9).

Muscle breakdown or proteolysis is driven by two pathways: ubiquitin–proteasome pathway (UPP) and the autophagy system. UPP is the major proteolysis pathway. Muscle protein is conjugated with ubiquitin, then degraded by 26S proteasome and removed. UPP can be induced by inactivity, injury, and inflammation driven by tumor necrosis factor (TNF), whereas it can be inhibited by protein kinase B. Autophagy contributes to cell homeostasis removing misfolded proteins and damaged organelles by the formation of autophagasome, which in turn delivers its contents to lysosomes for degradation. A factor in controlling autophagy rate is mTOR. Rapamycin has been demonstrated to stimulate autophagy by inhibiting mTOR. Thus myostatin, which inhibits mTOR, probably increases muscle proteolysis as a consequence of autophagy stimulation. An ongoing trial of leucine-enriched essential amino acid mixture seeks to demonstrate a reduction in autophagia and thus improve hepatic sarcopenia as leucine is a direct stimulant of mTOR (Clinical trials identifier NCT03208868).

Potential Mechanisms of Sarcopenia

Dysregulated muscle proteostasis in ESLD may result from a number of factors including cirrhosis being a metabolic starvation disorder, hormonal dysfunction (i.e., reduced testosterone), defective ureagenesis, alterations in branched chain amino acids, and a chronic inflammatory response to endotoxemia leading to elevated levels of TNF. This leads to an imbalance between muscle protein synthesis and proteolysis being disrupted in favor of proteolysis. As one may expect, there is marked interplay between the various potential mechanisms of sarcopenia. A considerable amount of research has concentrated on defective ureagenesis leading to elevated levels of ammonia or hyperammonemia. Ammonia is derived from purine, amino acid, and gut bacteria metabolism. In the face of a reduction of the number of effective hepatocytes, which are metabolically distressed, as a consequence of cirrhosis and portal hypertension leading to portocaval shunting, ammonia levels are raised in cirrhosis to cytotoxic levels. As the cirrhotic liver is unable to metabolize ammonia, skeletal muscle uptake of ammonia increases where it is converted to glutamine via a glutamate pathway. Within the skeletal muscle, excess ammonia induces transregulation of myostatin by a NF-kappa-mediated mechanism (10). Myostatin is a primary inhibitor of protein synthesis and increases autophagy leading to accelerated sarcopenia. It is well established that myostatin levels are increased in cirrhosis (11).

The resultant detoxification of ammonia within the mitochondria leads to high levels of glutamine in the circulation. This is utilized by other peripheral tissues generating another source of ammonia thus maintaining the need for skeletal muscle to continually metabolize it. The biochemical step to convert ammonia to glutamate requires the tricarboxylic acid cycle intermediary alpha-ketoglutarate. The constant demand for it eventually leads to its depletion resulting in mitochondrial dysfunction and consequently decreased protein synthesis. In addition, the mitochondria become increasingly leaky generating reactive oxidative species further inducing autophagy and proteolysis (12, 13). Hyperammonemia, and the resultant intracellular amino acid deficiency, further stresses the cell resulting in a reduction of mRNA translation and protein synthesis, which occurs via a eukaryotic initiation factor (eIF2) alpha kinase, general control nondepressed two (GCN2) pathway (12–15).

Due to cirrhosis being a state of accelerated starvation, and with the reduction in available branched chain amino acids (BCCA) because of their role in anaplerosis, it has also been suggested that muscle synthesis is restricted as amino acids are diverted to other cells for the synthesis of other critical amino acids such as albumin (16). Reduced cellular amino acid concentrations also activate increased skeletal muscle autophagy in cirrhosis (17). Hormonal disarray may also play a role in sarcopenia. Both testosterone and growth hormone are known to inhibit myostatin expression and signaling (18, 19). In cirrhosis, both are reduced and therefore may contribute to decreased muscle protein synthesis (20, 21).

In addition to being a starvation disorder, cirrhosis is also a state of chronic endotoxemia leading to increased circulating levels of TNF. TNF has been shown to impair muscle synthesis, activate autophagy, and inhibit hormones such as growth hormone and IGF-1 (22–24).

Diagnosis of Sarcopenia in Cirrhosis

A full dietary survey should be undertaken to address any concomitant malnutrition. Bioelectrical impedance analysis, dual energy X-ray absorptiometry (DEXA), and air displacement plethismography reflect indirect measures of muscle mass (25). CT and MRI are now the recommended investigations offering both sensitive and specific measure of adiposity and muscle mass. Measurement of peripheral muscle mass is not acceptable due to changes in muscle bulk associated with activity. Evaluation of psoas and paraspinal muscles using CT at the level of the third lumbar vertebra (L3) is a more reproducible means of sequentially following muscle bulk.

The definition of sarcopenia in patients with cirrhosis lacks a consensus regarding adequate cut-off values. Most studies defining sarcopenia use the L3 skeletal mass index cut-off values suggested by Prado (L3 SMI: ≤ 38.5 cm^2/m^2 for women and ≤ 52.4 cm^2/m^2 for men) (26). However, both CT and MRI have limited access in routine practice (27). Recently, the use of the combination of body mass index and thigh muscle thickness measured by ultrasound has been shown to be almost as good as CT in assessing cirrhotic sarcopenia and may offer a cheaper more accessible means of diagnosing sarcopenia (28).

Potential Treatments of Sarcopenia

There are no definitive therapies to reverse cirrhotic sarcopenia. Attempts at improving muscle mass by means of nutritional support, increasing exercise, and correcting hormonal disarray have proved disappointing although reducing ammonia levels and myostatin levels are promising in some studies.

General nutritional support

The caloric and protein intake in ESLD is usually reduced due to alterations in taste, anorexia, salt restriction, and impaired gut motility leading to a relative malabsorptive state (29). This lack of intake accelerates the state of metabolic starvation in patients. Several studies of enteral and parenteral feeding have not shown any improvement in muscle mass, nutritional status, nitrogen retention, or survival (30). Only a single study of high energy–high protein supplementation was able to demonstrate significant nitrogen retention. The utilization of a multidisciplinary nutrition support team and patient education appears to benefit quality of life and improve survival (31). The timing of nutritional support appears to be important. Evidence suggests that a late evening snack and an early morning protein supplement are the most likely to stabilize muscle homeostasis (32). The amounts of caloric and protein intake are well documented in the European Association for Study of the Liver (EASL) Clinical Practice guidelines on nutrition in chronic liver disease (33).

Exercise

Exercise stimulates muscle protein synthesis through the activation of mTOR but whether this pathway in cirrhosis is inhibited by hyperammonemia and elevated myostatin is unknown. There is evidence that hyperammonemia alters muscle function by altering contractile function and increasing muscle fatigue in patients with ESLD (34). Exercise generates muscle ammonia, which may negate any potential muscle protein synthesis (35). Despite these theoretical considerations, a combination of moderate intensity resistance and endurance exercise may benefit sarcopenia in ESLD (36). A recent study has suggested that a combination of BCAA supplementation and walking exercise improved muscle volume and hand grip strength which if confirmed could be easily implemented (37).

Branched chain amino acid supplementation

In ESLD, it is well established that there is a decrease in BCAA and an increase in aromatic amino acids (AAA) which may contribute to hepatic encephalopathy (HE) (38, 39). The role of BCAA therapy in HE is not established with some trials showing no benefit, while a recent Cochrane review favors benefit (40–42). A further study of BCAA supplementation in HE suggests that minimal HE can be prevented and interestingly muscle mass can be recovered (43). BCAA may be of benefit by acting as a substrate for anaplerosis in the alpha-ketoglutamate, Glutamine–glutamate pathway in muscle, and thereby remove ammonia. A further potential mechanism of BCAA therapy maybe to act as an inhibitor of the amino acid deficiency sensor GCN2 and reverse eIF2 phosphorylation leading to an increase in muscle synthesis (44). The specific use of leucine-rich amino acid supplementation stimulates mTOR activation leading to higher rate of protein synthesis via messenger RNAs (mRNA) (45–47). If mTOR signaling is impaired, autophagy is increased in cirrhosis, and it has been shown that this can be reversed by an enriched leucine BCAA supplementation. In addition, the study suggested the reversal of the GNC2/eIF2 pathway (48).

Anabolic Hormones

Testosterone, growth hormone, and insulin-like growth factor-1 (IGF-1) are known to influence muscle protein synthesis by activating mTOR and suppressing myostatin (49). These anabolic hormones are reduced in cirrhosis (50) but studies have not shown any definitive benefit in cirrhotic sarcopenia. In a rat model of cirrhosis, IGF-1 treatment has been shown a decrease in myostatin and improved nitrogen retention (51, 52). Recently, Nutmeg extract has been demonstrated to increase skeletal muscle mass in the elderly acting via the IGF-1, protein kinase B(AKT), and mTOR pathway inhibiting autophagy (53). Whether this could be applied to ESLD patients with sarcopenia begs further clinical studies. Testosterone trials in reversing sarcopenia have been inconclusive, although one small study demonstrated improved hand grip (54). A further study of men with cirrhosis was able to show an increase in bone mass and muscle mass, and a reduction in the fat mass (55).

Ammonia Lowering Therapy

Reducing ammonia levels may potentially reverse sarcopenia. However, sarcopenia continues to be a problem following liver transplantation which should correct the metabolic changes of ESLD (56) It has been suggested that the use of post-transplant immunosuppressant drugs, such as cyclosporine A and mTOR inhibitors, may be responsible for the ongoing sarcopenia (3, 57). In a recent animal model of portal hypertension, the use of rifaximin and L-orthenine L-aspartate (LOLA) for 4 weeks was seen to restore muscle proteostasis and reverse sarcopenia. The treatment was seen to downregulate the ammonia-induced myostatin production, reverse autophagy, and partially reverse GCN2/eIF2 pathway activity. As lowering of ammonia is an established therapy for hepatic encephalopathy, long-term clinical studies of such therapy are now indicated (12).

Myostatin inhibition

Myostatin inhibitors have the potential to promote muscle protein synthesis although no human data are available. Recently, antibodies to myostatin and its precursor promyostatin have been shown in rats and non-human primates to inhibit myostatin activity and induce muscle anabolic activity. Similar results in non-human primates have been found with domagrozumab therapy (58, 59). The use of recombinant follistatin-288 has been shown to promote growth of skeletal muscle (9).

Prognosis of Sarcopenia

The overall rate of mortality in cirrhotic patients is 12.5 in every 100,000 patients (60). With the onset of sarcopenia, there is a threefold increase in mortality compared to cirrhotic patients without sarcopenia (61). Sarcopenia is an independent prognostic indicator for patients awaiting liver transplantation with estimated survival rates at 1, 2, and 3 years being 63%, 51%, and 51%, respectively, compared to nonsarcopenic patients with survival rates of 79%, 74%, and 70% over a similar period (62).

A number of studies have identified sarcopenia to be a prognostic factor in the increased mortality of patients awaiting liver transplantation. In a study of 232 consecutive transplant recipients, sarcopenia increased the length of hospital stay, intensive care unit (ICU) stay, and 12-month mortality; 6% of the sarcopenic patients did not survive the 12-month period (63). A meta-analysis comparing patients with sarcopenia and non-sarcopenia demonstrated an increased mortality by 3.25% for patients with ESLD and sarcopenia. The sarcopenia patients also had an increased complication rate in post-transplant infections, sepsis, and mechanical ventilation periods compared to non-sarcopenia patients who were less likely to experience these complications. The analysis highlights that due to sarcopenia's significant influence on mortality and complications, it is an important prognostic factor, independent of the current model of end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores used (4).

A large retrospective study of sarcopenia-related ESLD (64) found that paraspinal muscles index (PSMI) seems to be the most reliable diagnostic aid in predicting transplant outcomes. Its use not only predicts death but also estimates associated complications for patients on the transplant

waiting list. This study supports Kalafateli et al.'s paper, and in that it calculates the improved outcomes of patients per unit of improved muscle mass.

The traditional MELD score does not incorporate sarcopenia as a factor of assessment. The evidence above and many other existing studies support that sarcopenia is, in itself, a prognostic indicator of survival for ESLD patients. A more recent modified version, known as the MELD-sarcopenia score, has been proposed, offering a better prognostic value for patients awaiting or undergoing liver transplant. Therefore, consideration and management of skeletal muscle may improve transplantation outcomes.

Conclusion

Sarcopenia is a common and significant complication of cirrhosis. It is a prevalent and important issue to address in patient's awaiting liver transplant, as sarcopenia greatly increases mortality. There have been multiple hypotheses proposed regarding the mechanism(s) underlying sarcopenia in order to determine an effective treatment. This includes defective ureagenesis with ammonia elevation, alterations in BCAA, and chronic inflammatory response with the presence of elevated TNF leading to increased proteolysis. Based on these hypotheses, interventions have been attempted with some promising results, including nutrition support, exercise focused on resistance and endurance, and BCAA supplementation. Targeting ammonia has also shown to have benefits on sarcopenia, especially with the use of rifaximin and LOLA restoring muscle proteostasis, potentially reversing sarcopenia. Although transplant remains the only curative treatment, patients with significant sarcopenia are less likely to survive transplant. Efforts should focus on improving muscle mass and nutrition in these patients prior to surgery. Increasing the awareness of sarcopenia should improve the prognosis and quality of life of patients with ESLD.

Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

References

1. Tsochatzis E, Bosch J, Burroughs A. Liver cirrhosis. Lancet. 2014;383(9930):1749–61. https://doi.org/10.1016/S0140-6736(14)60121-5
2. Bernal W, Martin-Mateos R, Lipcsey M, Tallis C, Woodsford K, Mcphail M, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. Liver Transplantation. 2013;20(1):54–62. https://doi.org/10.1002/lt.23766
3. Dasarathy S. Consilience in sarcopenia of cirrhosis. J Cachexia Sarcopenia Muscle. 2012;3(4):225–37. https://doi.org/10.1007/s13539-012-0069-3
4. Kim G, Kang S, Kim M, Baik S. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. PLoS One. 2017;12(10):e0186990. https://doi.org/10.1371/journal.pone.0186990
5. Benjamin J, Shasthry V, Kaal C, Anand L, Bhardwaj A, Pandit V, et al. Characterization of body composition and definition of sarcopenia in patients with alcoholic cirrhosis: A computed tomography based study. Liver Int. 2017;37(11):1668–74. https://doi.org/10.1111/liv.13509
6. Bryant R, Ooi S, Schultz C, Goess C, Grafton R, Hughes J, et al. Low muscle mass and sarcopenia: Common and predictive of osteopenia in inflammatory bowel disease. Aliment Pharmacol Therapeut. 2015;41(9):895–906. https://doi.org/10.1111/apt.13156
7. Ito N, Ruegg U, Takeda S. ATP-induced increase in intracellular calcium levels and subsequent activation of mTOR as regulators of skeletal muscle hypertrophy. Int J Mol Sci. 2018;19(9):2804. https://doi.org/10.3390/ijms19092804
8. Drummond M, Dreyer H, Fry C, Glynn E, Rasmussen B. Nutritional and contractile regulation of human skeletal muscle protein synthesis and mTORC1 signaling. J Appl Physiol. 2009;106(4):1374–84. https://doi.org/10.1152/japplphysiol.91397.2008
9. Castonguay R, Lachey J, Wallner S, Strand J, Liharska K, Watanabe A, et al. Follistatin-288-Fc fusion protein promotes localized growth of skeletal muscle. J Pharmacol Exp Therapeut. 2018;368(3):435–45. https://doi.org/10.1124/jpet.118.252304
10. Qiu J, Thapaliya S, Runkana A, Yang Y, Tsien C, Mohan M, et al. Hyperammonemia in cirrhosis induces transcriptional regulation of myostatin by an NF- B-mediated mechanism. Proc Natl Acad Sci. 2013;110(45):18162–7. https://doi.org/10.1073/pnas.1317049110
11. Nishikawa H, Enomoto H, Ishii A, Iwata Y, Miyamoto Y, Ishii N, et al. Elevated serum myostatin level is associated with worse survival in patients with liver cirrhosis. J Cachexia Sarcopenia Muscle. 2017;8(6):915–25. https://doi.org/10.1002/jcsm.12212
12. Kumar A, Davuluri G, Silva R, Engelen M, Ten Have G, Prayson R, et al. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. Hepatology. 2017;65(6):2045–58. https://doi.org/10.1002/hep.29107
13. Davuluri G, Krokowski D, Guan B, Kumar A, Thapaliya S, Singh D, et al. Metabolic adaptation of skeletal muscle to hyperammonemia drives the beneficial effects of l-leucine in cirrhosis. J Hepatol. 2016;65(5):929–37. https://doi.org/10.1016/j.jhep.2016.06.004
14. Dasarathy S, Hatzoglou M. Hyperammonemia and proteostasis in cirrhosis. Curr Opin Clin Nutr Metab Care. 2018;21(1):30–6. https://doi.org/10.1097/MCO.0000000000000426
15. Anda S, Zach R, Grallert B. Activation of Gcn2 in response to different stresses. PLoS One. 2017;12(8):e0182143.https://doi.org/10.1371/journal.pone.0182143
16. Glass C, Hipskind P, Tsien C, Malin S, Kasumov T, Shah S, et al. Sarcopenia and a physiologically low respiratory quotient in patients with cirrhosis: A prospective controlled study. J Appl Physiol. 2013;114(5):559–65. https://doi.org/10.1152/japplphysiol.01042.2012
17. Breuillard C, Cynober L, Moinard C. Citrulline and nitrogen homeostasis: An overview. Amino Acids. 2015;47(4):685–91. https://doi.org/10.1007/s00726-015-1932-2
18. Liu W, Thomas S, Asa S, Gonzalez-Cadavid N, Bhasin S, Ezzat S. Myostatin is a skeletal muscle target of growth hormone anabolic action. J Clin Endocrinol Metabol. 2003;88(11):5490–6. https://doi.org/10.1210/jc.2003-030497

19. Lakshman K, Bhasin S, Corcoran C, Collins-Racie L, Tchistiakova L, Forlow S, et al. Measurement of myostatin concentrations in human serum: Circulating concentrations in young and older men and effects of testosterone administration. Mol Cell Endocrinol. 2009;302(1):26–32. https://doi.org/10.1016/j.mce.2008.12.019
20. Handelsman D, Strasser S, McDonald J, Conway A, McCaughan G. Hypothalamic-pituitary-testicular function in end-stage non-alcoholic liver disease before and after liver transplantation. Clin Endocrinol. 1995;43(3):331–7. https://doi.org/10.1111/j.1365-2265.1995.tb02040.x
21. Dasarathy S, Mullen K, Dodig M, Donofrio B, McCullough A. Inhibition of aromatase improves nutritional status following portacaval anastomosis in male rats. J Hepatol. 2006;45(2):214–20. https://doi.org/10.1016/j.jhep.2006.02.016
22. Lang C, Frost R, Nairn A, MacLean D, Vary T. TNF-α impairs heart and skeletal muscle protein synthesis by altering translation initiation. Am J Physiol Endocrinol Metabol. 2002;282(2):E336–47. https://doi.org/10.1152/ajpendo.00366.2001
23. Keller C, Fokken C, Turville S, Lünemann A, Schmidt J, Münz C, et al. TNF-α induces macroautophagy and regulates MHC class ii expression in human skeletal muscle cells. J Biol Chem. 2010;286(5):3970–80. https://doi.org/10.1074/jbc.M110.159392
24. Fernández-Celemín L, Pasko N, Blomart V, Thissen J. Inhibition of muscle insulin-like growth factor I expression by tumor necrosis factor-α. Am J Physiology Endocrinol Metabol. 2002;283(6):E1279–90. https://doi.org/10.1152/ajpendo.00054.2002
25. Peng S, Plank L, McCall J, Gillanders L, McIlroy K, Gane E. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: A comprehensive study. Am J Clin Nutr. 2007;85(5):1257–66. https://doi.org/10.1093/ajcn/85.5.1257
26. Prado C, Lieffers J, McCargar L, Reiman T, Sawyer M, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: A population-based study. Lancet Oncol. 2008;9(7):629–35. https://doi.org/10.1016/S1470-2045(08)70153-0
27. Andersson K, Salomon J, Goldie S, Chung R. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol. 2008;6(12):1418–24. https://doi.org/10.1016/j.cgh.2008.08.005
28. Tandon P, Low G, Mourtzakis M, Zenith L, Myers R, Abraldes J, et al. A model to identify sarcopenia in patients with cirrhosis. Clin Gastroenterol Hepatol. 2016;14(10):1473–80.e3. https://doi.org/10.1016/j.cgh.2016.04.040
29. Dasarathy S. Nutrition and alcoholic liver disease. Clin Liver Dis. 2016;20(3):535–50. https://doi.org/10.1016/j.cld.2016.02.010
30. Plauth M, Bernal W, Dasarathy S, Merli M, Plank L, Schütz T, et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr. 2019;38(2):485–521. https://doi.org/10.1016/j.clnu.2018.12.022
31. Iwasa M, Iwata K, Hara N, Hattori A, Ishidome M, Sekoguchi-Fujikawa N, et al. Nutrition therapy using a multidisciplinary team improves survival rates in patients with liver cirrhosis. Nutrition. 2013;29(11–12):1418–21. https://doi.org/10.1016/j.nut.2013.05.016
32. Rivera Irigoin R, Abilés J. Soporte nutricional en el paciente con cirrosis hepática. Gastroenterología y Hepatología. 2012;35(8):594–601. https://doi.org/10.1016/j.gastrohep.2012.03.001
33. Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L, et al. EASL clinical practice guidelines on nutrition in chronic liver disease. J Hepatol. 2019;70(1):172–93. https://doi.org/10.1016/j.jhep.2018.06.024
34. McDaniel J, Davuluri G, Hill E, Moyer M, Runkana A, Prayson R, et al. Hyperammonemia results in reduced muscle function independent of muscle mass. Am J Physiol Gastrointest Liver Physiol. 2016;310(3):G163–70. https://doi.org/10.1152/ajpgi.00322.2015
35. Dietrich R, Bachmann C, Lauterburg B. Exercise-induced hyperammonemia in patients with compensated chronic liver disease. Scand J Gastroenterol. 1990;25(4):329–34. https://doi.org/10.3109/00365529009095494
36. Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. Hepatology. 2017;65(4):1293–305. https://doi.org/10.1002/hep.28992
37. Hiraoka A, Michitaka K, Kiguchi D, Izumoto H, Ueki H, Kaneto M, et al. Efficacy of branched-chain amino acid supplementation and walking exercise for preventing sarcopenia in patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2017;29(12):1416–23. https://doi.org/10.1097/MEG.0000000000000986
38. Campollo, O., Sprengers, D., McIntyre, N. The BCAA/AAA ratio of plasma amino acids in three different groups of cirrhotics. Rev Invest Clin. 1992; 44(4):513–18.
39. Tajiri K, Shimizu Y. Branched-chain amino acids in liver diseases. Transl Gastroenterol Hepatol. 2018;3:47–47. https://doi.org/10.21037/tgh.2018.07.06
40. Gluud L, Dam G, Les I, Marchesini G, Borre M, Aagaard N, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2015;(2):CD001939. https://doi.org/10.1002/14651858.CD001939.pub4
41. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005;3(7):705–13. https://doi.org/10.1016/S1542-3565(05)00017-0
42. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: A double-blind, randomized trial. Gastroenterology. 2003;124(7):1792–801. https://doi.org/10.1016/S0016-5085(03)00323-8
43. Les I, Doval E, García-Martínez R, Planas M, Cárdenas G, Gómez P, et al. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: A randomized study. Am J Gastroenterol. 2011;106(6):1081–8. https://doi.org/10.1038/ajg.2011.9
44. Zhang P, McGrath B, Reinert J, Olsen D, Lei L, Gill S, et al. The GCN2 eIF2 kinase is required for adaptation to amino acid deprivation in mice. Mol Cell Biol. 2002;22(19):6681–8. https://doi.org/10.1128/MCB.22.19.6681-6688.2002
45. Anthony J, Yoshizawa F, Anthony T, Vary T, Jefferson L, Kimball S. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway. J Nutr. 2000;130(10):2413–19. https://doi.org/10.1093/jn/130.10.2413
46. Anthony T, Anthony J, Yoshizawa F, Kimball S, Jefferson L. Oral administration of leucine stimulates ribosomal protein mRNA translation but not global rates of protein synthesis in the liver of rats. J Nutr. 2001;131(4):1171–6. https://doi.org/10.1093/jn/131.4.1171

47. Dardevet D, Sornet C, Balage M, Grizard J. Stimulation of in vitro rat muscle protein synthesis by leucine decreases with age. J Nutr. 2000;130(11):2630–5. https://doi.org/10.1093/jn/130.11.2630
48. Tsien C, Davuluri G, Singh D, Allawy A, Ten Have G, Thapaliya S, et al. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. Hepatology. 2015;61(6):2018–29. https://doi.org/10.1002/hep.27717
49. Marcell T, Harman S, Urban R, Metz D, Rodgers B, Blackman M. Comparison of GH, IGF-I, and testosterone with mRNA of receptors and myostatin in skeletal muscle in older men. Am J Physiol Endocrinol Metabol. 2001;281(6):E1159–64. https://doi.org/10.1152/ajpendo.2001.281.6.E1159
50. Moctezuma-Velázquez C, Low G, Mourtzakis M, Ma M, Burak K, Tandon P, et al. Association between low testosterone levels and sarcopenia in cirrhosis: A cross-sectional study. Ann Hepatol. 2018;17(4):615–23. https://doi.org/10.5604/01.3001.0012.0930
51. Picardi A, de Oliveira A, Muguerza B, Tosar A, Quiroga J, Castilla-Cortázar I, et al. Low doses of insulin-like growth factor-I improve nitrogen retention and food efficiency in rats with early cirrhosis. J Hepatol. 1997;26(1):191–202. https://doi.org/10.1016/S0168-8278(97)80026-8
52. Lang C, Frost R, Svanberg E, Vary T. IGF-I/IGFBP-3 ameliorates alterations in protein synthesis, eIF4E availability, and myostatin in alcohol-fed rats. Am J Physiol Endocrinol Metabol. 2004;286(6):E916–26. https://doi.org/10.1152/ajpendo.00554.2003
53. Pratiwi Y, Lesmana R, Goenawan H, Sylviana N, Setiawan I, Tarawan V, et al. Nutmeg extract increases skeletal muscle mass in aging rats partly via IGF1-AKT-mTOR pathway and inhibition of autophagy. Evid Base Compl Alternative Med. 2018;2018:1–8. https://doi.org/10.1155/2018/2810840
54. Yurci A, Yucesoy M, Unluhizarci K, Torun E, Gursoy S, Baskol M, et al. Effects of testosterone gel treatment in hypogonadal men with liver cirrhosis. Clin Res Hepatol Gastroenterol. 2011;35(12):845–54. https://doi.org/10.1016/j.clinre.2011.09.005
55. Sinclair M, Grossmann M, Hoermann R, Angus P, Gow P. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial. J Hepatol. 2016;65(5):906–13. https://doi.org/10.1016/j.jhep.2016.06.007
56. Tsien C, Garber A, Narayanan A, Shah S, Barnes D, Eghtesad B, et al. Post-liver transplantation sarcopenia in cirrhosis: A prospective evaluation. J Gastroenterol Hepatol. 2014;29(6):1250–7. https://doi.org/10.1111/jgh.12524
57. Dasarathy S. Posttransplant sarcopenia: An underrecognized early consequence of liver transplantation. Dig Dis Sci. 2013;58(11):3103–11. https://doi.org/10.1007/s10620-013-2791-x
58. Pirruccello-Straub M, Jackson J, Wawersik S, Webster M, Salta L, Long K, et al. Blocking extracellular activation of myostatin as a strategy for treating muscle wasting. Sci Rep. 2018;8:2292. https://doi.org/10.1038/s41598-018-20524-9
59. St. Andre M, Johnson M, Bansal P, Wellen J, Robertson A, Opsahl A, et al. A mouse anti-myostatin antibody increases muscle mass and improves muscle strength and contractility in the mdx mouse model of Duchenne muscular dystrophy and its humanized equivalent, domagrozumab (PF-06252616), increases muscle volume in cynomolgus monkeys. Skeletal Muscle. 2017;7(1):25. https://doi.org/10.1186/s13395-017-0141-y
60. FastStats [Internet]. Cdc.gov. 2019 [cited 2019 Mar 11]. Available from: https://www.cdc.gov/nchs/fastats/liver-disease.htm
61. Kittiskulnam P, Chertow G, Carrero J, Delgado C, Kaysen G, Johansen K. Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. Kidney Int. 2017;92(1):238–47. https://doi.org/10.1016/j.kint.2017.01.024
62. Tandon P, Ney M, Irwin I, Ma M, Gramlich L, Bain V, et al. Severe muscle depletion in patients on the liver transplant wait list: Its prevalence and independent prognostic value. Liver Transplant. 2012;18(10):1209–16. https://doi.org/10.1002/lt.23495
63. Kalafateli M, Mantzoukis K, Choi Yau Y, Mohammad A, Arora S, Rodrigues S, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for end-stage liver disease score. J Cachexia Sarcopenia Muscle. 2016;8(1):113–21. https://doi.org/10.1002/jcsm.12095
64. Engelmann C, Schob S, Nonnenmacher I, Werlich L, Aehling N, Ullrich S, et al. Loss of paraspinal muscle mass is a gender-specific consequence of cirrhosis that predicts complications and death. Aliment Pharmacol Therapeut. 2018;48(11–12):1271–81. https://doi.org/10.1111/apt.15026